62. The plant cell of claim 43 wherein the cell is a monocotyledonous plant cell.

63. The plant cell of claim 43 derived from an algal plant.

REMARKS

Claims 21-40, 43, 50, 54-63 and 69-80 are currently pending following entry of the instant Amendment. Briefly, claim 21 and its dependent claims are directed to a plant comprising plant cells containing nucleotide sequences encoding one or more biologically functional multimeric proteins not normally produced by the plant, and biologically functional multimeric proteins encoded by the nucleotide sequences formed by assembly of said polypeptides in the plant cell. These claims recite the requirement that each nucleotide sequence encoding a polypeptide of the multimeric protein encodes a leader sequence forming a secretion signal that is cleaved from the polypeptide following proteolytic processing. In dependent claims, the multimeric protein comprises an immunoglobulin.

Claim 43 and its dependent claims are directed to a plant cell that contains nucleotide sequences encoding a biologically functional multimeric protein which is an immunoglobulin molecule. The plant contains nucleotide sequences encoding an immunoglobulin heavy and light chain polypeptide wherein each polypeptide contains a leader sequence forming a secretion signal. The plant cell also contains immunoglobulin molecules encoded by the nucleotide sequences, wherein each leader sequence forms a secretion signal that is cleaved from the immunoglobulin heavy chain and light chain polypeptide following proteolytic processing, resulting in assembly of the antigen-specific immunoglobulin.

Thus, common to all the pending claims is for the multimeric protein to have a leader sequence for each polypeptide that forms a secretion signal which is cleaved following proteolytic processing. Also common is the requirement for assembly of the polypeptides in the plant cell resulting in formation of a multimer which is biologically functional multimer (i.e., "antigen-specific," in the case of immunoglobulin).

The amended claims and the newly added claims are fully supported by the specification, and do not introduce new matter. Claim 21 finds basis in the application, for example, at page 15, lines 8-14 ("first and second polypeptides associate together in such a way as to assume a biologically functional confirmation"). Claim 43 finds basis, for example, at page 15, lines 8-21, and page 73-77 (Examples 7 and 8).

AMENDMENT OF THE SPECIFICATION

Applicants have amended the cross reference section in the first paragraph of the specification, as noted above. Accordingly, the status of all parent priority applications/patents have been updated.

NON-STATUTORY DOUBLE PATENTING

Claims 21-64 and 65-68 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 21-30 and 36-37 of copending Application No. 09/199,534;

Claims 21-40, 42-64 and 65-68 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 21 and 32-78 of copending Application No. 09/200,657;

Claims 21-40, 42-64 and 65-68 have been rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 6-12 of U.S. Patent No. 5,959,177;

Claims 21-40, 42-64 and 65-68 have been rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 1-5 of U.S. Patent No. 5,202,422; and

Claims 21-40, 42-64 and 65-68 have been rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 1-7 of U.S. Patent No. 5,639,947.

As discussed in the previous response (Paper No. 8, pages 4-6), Applicants respectfully disagree and traverse the rejection. In the interests of furthering prosecution of the case, however, the above mentioned disclaimers have been previously filed. Applicants reserve the right to later withdraw the disclaimer depending on circumstances.

REJECTION UNDER 35 U.S.C. § 102 OVER DÜRING

The rejection of claims 21-40 and 42-68 under 35 U.S.C. § 102(b) as being allegedly anticipated by Düring (Dissertation) is respectfully traversed. Claims 42, 44-49, 51-53, and 64-68 have been cancelled herein, rendering the rejection moot as to these claims. All reference herein to the During dissertation are to the English language translation prepared by Ralph McElroy Translation Company, 910 West Avenue, Austin Texas (Job No. 1596-81522). The arguments below are supported by a declaration pursuant to 37 C.F.R. §1.132 by Richard Lerner, M.D., President of the Scripps Research Institute ("the Lerner declaration"), copy attached herewith.

Relevant Law

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. In re Spada F.2d, 15 USPQ2d 1655 (Fed. Clr, 1990), In re Bond, F.2d , 15 USPQ 1566 (Fed. Clr. 1990). Furthermore, it is incumbent on Examiner to identify wherein each and every facet of the claimed invention is disclosed. Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co., 730 F.2d,1452, 221 USPQ 481 (Fed. Cir. 1984).

Argument

A. The claims are not anticipated (or obvious) because the During dissertation uses a different strategy from the claimed invention.

During fails to disclose or otherwise teach the elements of claim 21 and 43 and their dependent claims including the requirement the multimeric protein to have a leader sequence for each polypeptide that forms a secretion signal which is cleaved following proteolytic processing and the requirement for assembly of the polypeptides in the plant cell resulting in formation of a multimer which is biologically functional multimer (i.e., "antigen-specific" in the case of an immunoglobulin). The strategy used by During for

expressing a two chain multimer (i.e., a light and heavy chain) differs from this claimed requirement. In the During dissertation, the nucleic acid encoding the barley alpha amylase signal sequence was inserted directly 5' to the end of the DNA encoding the amino terminal end of the mature heavy chain. In the case of the light chain, however, During included nucleic acid encoding three additional amino acids (Gly-Ser-Met) between the DNA encoding the leader sequence and the DNA encoding the mature amino terminus of the light chain. Lerner declaration, ¶9. The additional amino acids that would be encoded at the 3' end of the light chain leader sequence constructed by During were unusual, according to Lerner, and it was not clear what effect additional amino acids would have on final processing of the leader. Lerner declaration, ¶¶10 and 11. In is now clear from the art that mutations introduced in the vicinity of a cleavage site have the potential to adversely influence signal processing. Lerner declaration, ¶11. In the opinion of Lerner, During's strategy of adding additional amino acids residues to the cleavage site for the light chain leader likely obscured substrate recognition causing cleavage site ambiguity. Lerner declaration, ¶¶11 and 12.

Thus, it is respectfully submitted that these facts alone evidence that the During dissertation does not teach the claimed requirement for proteolytic processing of a leader sequence and assembly of the heavy and light polypeptides to form an antigen-specific immunoglobulin (or biologically functional multimer) in the plant cell. It is respectfully submitted, therefore, that no substantive foundation exists upon which to find the claims anticipated (or obvious) over During and the rejection fails on this basis alone.

B. The claims are not anticipated (or obvious) because During's assertion of successful antibody expression in plants would not have been believed by the ordinary skilled artisan or, in the alternative, the During dissertation is non-enabling.

1. <u>There was a prejudice in the art against the possibility that plant cells could be used to produce an antigen-specific immunoglobulin</u>

Any analysis of the of the prior art in the context of an anticipation or obviousness rejection must be made from the perspective of the ordinary skilled artisan at the proper time frame. The Lerner declaration goes to great length to properly ascertain

this perspective at the time period beginning from the alleged publication date of the During dissertation (July 1988) and up to the earliest filing date of the above captioned patent application (October 27, 1989). The analysis shows that there is strong evidence at the relevant time period for the existence of a prejudice in the art against the possibility of using plant cells to process and assemble an antigen-specific immunoglobulin. According to Lerner, it was appreciated by the early 1980s that the biology of antibody expression was complex and varied with the maturation state of the B cell. For example, rearrangement of immunoglobulin chain variable region encoding gene segments is required to form a functional immunoglobulin gene, and rearrangement of the heavy chain occurs before rearrangement of the light chain. In fact, there is an early stage B cell known as the "pre-B cell," characterized in having a productively rearranged heavy chain V gene but not a rearranged light chain V gene. Lerner declaration, ¶3. In contrast, a later stage of B cells is known (i.e., "young B cell), characterized in having both the heavy and the light chain V genes productively rearranged and in expressing a full-sized immunoglobulin on the cell surface. *Id.*

Lerner goes on to explain that antibody expression in B cells was understood to be further complicated by the involvement of the BiP protein, known to be involved in heavy chain processing. Lerner declaration, ¶3. A phenomenon called heavy chain toxicity also was appreciated at the time but its mechanism was unknown. Lerner declaration, ¶4. According to Lerner, by the mid 1980s, a prejudice had taken hold in the art against the notion that antigen-specific immunoglobulins could be produced in cells other than mammalian B cells. *Id.*

Although Lerner notes the existence of reports describing expression of an assembled antibody in two microorganisms (i.e., *Saccharomyces cerevisiae* and *E. coli*) he provides substantial reasoning for why the prevailing prejudice in the art would still have existed with respect to producing antigen-specific immunoglobulin in plant cells. Lerner declaration, ¶7. For example, Lerner notes that plant cells were known to be different from mammalian cells and from microorganisms such as *Saccharomyces cerevisiae* and *E. coli* not only in having a cell wall but also in features related to protein secretion. In addition, Lerner notes that it was not known at the time whether plant cells contained a

BiP protein or a functionally equivalent analogue. Lerner concludes from his review of the field that:

> [T]here was a sound basis for a real prejudice in the art against using plants to produce a processed and assembled immunoglobulin which is antigen specific around the time of the During dissertation (*circa* 1988/1989). Were this not the case, then Applicant's invention clearly would not have been roundly hailed in both the scientific literature and in the general press as a significant scientific discovery and medical breakthrough.

Lerner declaration, ¶8 (footnotes removed). It stands to reason, therefore, that the ordinary skilled artisan in the 1988/1989 time frame would have applied this prejudice to any claim purporting to demonstrate processing and assembly of an antigen-specific immunoglobulin in plant cells and would not have accepted such claim unless the proof was well founded. It is respectfully submitted that the teachings of the During declaration with respect to the rejection, must be viewed in light of this prejudice.

2. During's experimental results allegedly supporting immunoglobulin expression are internally inconsistent and are lacking in critical controls

During initially made a light chain only expression vector and evaluated whether plant cells transfected with this vector could express light chains. During, however, failed to detect light chain production in the cells (During dissertation, p. 80, line 2). According to Lerner, this fact would have been disturbing to the ordinary skilled artisan because light chain alone is readily expressed in B cells, and even if During's cells were making a small amount of light chain, albeit at a level below his detectability limit, this would complicate efforts to achieve and detect heavy-light chain assembly. Lerner further points out that an increased relative heavy chain expression, which under the circumstances might be necessary to obtain assembly in view of the low levels of expressed light chain, conceivably could result in toxicity if plant cells were susceptible to heavy chain toxicity, as was the case for mammalian B cells. These issues would have raised serious questions about During's chances for success and would have required additional proof for any alleged success to be accepted in the art.

Although During appreciated that his expression system was suboptimal, he proceeded to attempt expression of both a heavy and light chain from a single expression vector. Anticipating a threshold detectability problem, During utilized a pre-enrichment step prior to Western blotting (i.e., indirect Western) of transgenic plant extracts. Lerner declaration, ¶14. Lerner points out that During's need for an indirect Western also would have been disturbing to the ordinary skilled artisan because direct Western blotting was known to be a very sensitive technique that had previously been successfully used to demonstrate foreign host expression (including plant expression of antibodies as disclosed in the instant patent application). *Id.*

The Examiner is referred to the Lerner declaration § 15 for details of During's indirect Western results. It is significant that During now observes light chain detection with the dual chain vector (but not with the light only vector used earlier) but was unable to detect heavy chains by either direct or indirect Western blotting. *Id.* During's assertion that he has detected the presence of assembled B1-8 antibody in the plant cells is based, according to Lerner, on faulty circular logic.

> To conclude as he does from the Western results that assembled B1-8 antibody was present in the plant extract, During must infer that which he is attempting to prove, that fully assembled antibody must have been present in the extract for light chain to have been enriched following binding to the NP hapten immunoabsorbent. As will be seen below, this faulty circular reasoning is open to alternative explanations that directly conflict with During's conclusion.

Lerner declaration, ¶ 15. Lerner goes on to discuss numerous other reasonable explanations for the results that During did not address, let alone attempt to exclude. Notably, During fails to exclude the real possibility that light chain may have been enriched by the NP immunoabsorbent even if the light chain were not assembled with a heavy chain. During's failure to detect heavy chains by direct and indirect Western blotting is consistent with this possibility. As summarized by Lerner, there was much that During could have done (but failed to do) to exclude alternative artifactual explanations for his Western blotting data.

> For example, During could have directly demonstrated that heavy chain was absolutely required for light chain binding during the pre-enrichment step. Alternatively, or in addition, During could have used biosynthetic radiolabeling of plant cells in combination with Western blotting to prove that a heavy chain was in fact co-enriched with light chain. This method is well known in the art and was previously used to demonstrate foreign protein expression. Biosynthetic radiolabeling also helps to control for stripping of antibody during a low pH elution of an antibody immunoabsorbent column (i.e., the Ls136 adsorbent), a problem encountered with CNBr. Since During employed low pH elution and CNBr linkage, he should have provided controls to address this potential problem.

Lerner declaration, ¶ 16 (footnotes removed).

The During dissertation also evaluated antibody expression in his plants using a second technique referred to as "tissue printing." In this technique, a leaf is pressed against a membrane in order to bind proteins in the leaf to the membrane, and the membrane is probed by immunological reagents as in Western blotting. The During dissertation describes that light chain, heavy chain and "aggregated B1-8" antibody were detected by tissue printing. Although During asserts that these results support his conclusion of successful immunoglobulin assembly, Lerner believes that the tissue printing experiment are just as readily subject to alternative explanations because they lack controls which are essential to conclude that binding of an immunological reagent is antigen-specific. Lerner declaration, ¶ 17. Lerner bases his belief not only on his own experience as a scientist and immunologist for more than 30 years but also on the scientific literature. With respect to the latter, Lerner points out that the types of controls lacking in the During dissertation were used by others who previous to During demonstrated expression in yeast of the same B1-8 antibody that During was attempting to express in a plant. *Id.* (referring to Wood et al.) The few controls used by During in the tissue printing experiments were wholly insufficient under the circumstances to support During's assertion of success.

The During dissertation also includes immunogold electron microscopic analysis of his transgenic plant cells apparently with the same antibodies used in the Western blotting and tissue printing experiments. The Examiner is referred to the Lerner declaration § 18

for a detailed explanation of During's immunogold results. Lerner takes issues with During's conclusion that the immunogold results indicate successful assembly of the B1-8 antibody in plants. First, Lerner notes that the heavy chain again was not detected. In addition, Lerner points out that the areas of the cell that were immunogold labeled with the light chain reagent were not the same areas that were immunogold labeled with the Ac38 reagent (allegedly specific for an assembled B1-8 heavy and light chain). Lerner declaration, ¶ 18. It stands to reason that for assembly to have occurred, the two chains should be co-localized to at least one area of the cell. Furthermore, During failed to observe immunogold labeling in regions of the cell that one would normally have expected if antibody assembly were possible in plant cells. Lerner declaration, ¶ 19. Indeed, During observed immunoreactivity inexplicably in chloroplasts with the Ac38 antibody but not in the golgi apparatus or vesicles as others have observed previously for secreted proteins, including antibodies. Unusual results might be acceptable if plant cells were capable of antibody assembly in unique and previously unknown ways, however, unusual results cannot make up for the lack of controls in other experiments.

Lerner concludes that a person skilled in the art of immunology or protein expression, circa 1988/1989, would not have reasonably believed the assertion of the During dissertation that plant cells could be used to process and assemble an antigen-specific immunoglobulin. Lerner declaration, ¶ 22. Lerner bases this belief on During's failure to perform critical controls to support his conclusions and to explain his inconsistent results. Also, the Ac38 antibody which underlies virtually all of the support for During's assertion cannot be used, according to Lerner, to prove that NP antigen specific binding was present in transgenic plant cells. Lerner declaration, ¶ 22. Thus, even if During had done the proper antigen inhibition controls, more would have been needed, according to Lerner, to overcome the prejudice in the art. *Id.*

It is also Lerner's opinion that even if there were no prejudice in the art, During's conclusions would still not have been accepted. This view is based in part on Lerner's extensive experience as an editorial board member of more than ten scientific journals and an official reviewer for hundreds articles submitted for publication. Although During eventually published his antibody work in a peer-reviewed journal (i.e., 1990 article in

"Plant Molecular Biology"), this occurred after the inventors of the above-captioned application published their work (1989 article in "Nature"). Furthermore, as noted by Lerner, During's publication discusses the earlier publication by the inventors Hiatt and Hein at some length, describing it as a successful demonstration of antibody expression in plants. Lerner declaration, ¶ 22. In Lerner's opinion, had During not been able to support his work with the earlier publication by Hiatt and Hein, During's antibody expression experiments most likely would have been deemed unacceptable for publication. Lerner credits the inventors of the instant patent application, not During, as the first to convincingly demonstrate assembly of an antigen-specific immunoglobulin in plant cells.

It is respectfully submitted, therefore that the above demonstrates that the During dissertation fails to disclose or otherwise teach the elements of claim 21 and 43 and their dependent claims including the requirement for the multimeric protein to have a leader sequence for each polypeptide that forms a secretion signal which is cleaved following proteolytic processing, and the requirement for assembly of the polypeptides in the plant cell resulting in formation of a multimer which is a biologically functional multimer (i.e., "antigen-specific," in the case of immunoglobulin). Accordingly, because the During dissertation fails to disclose each and every element of the claimed invention, the claims are not anticipated under section 102(b) as a matter of law.

REJECTION UNDER 35 U.S.C. § 102 OVER GOODMAN

The rejection of claims 21-40 and 42-68 under 35 U.S.C. § 102(e) as being allegedly anticipated by Goodman (U.S. 4,956,282) is respectfully traversed. Claims 42, 44-49, 51-53, and 64-68 have been cancelled herein, rendering the rejection moot as to these claims.

As already discussed the claims require the multimeric protein to have a leader sequence for each polypeptide that forms a secretion signal which is cleaved following proteolytic processing, and the requirement for assembly of the polypeptides in the plant cell resulting in formation of a multimer which is biologically functional multimer (i.e., "antigen-specific," in the case of immunoglobulin). Thus, as presently constituted, the claimed invention requires that a secretion signal be used for both polypeptides of the multimer (a heavy and light chain for an immunoglobulin) and that there be proper

assembly of the polypeptide following proteolytic processing which removes the leader from each chain.

Goodman's teachings at best are limited to expressing gamma interferon, a lymphokine that is a single polypeptide not a multimer. Gamma interferon also is functionally distinct from immunoglobulin and, moreover, Goodman teaches virtually nothing about immunoglobulin expression in plants. In fact, it is respectfully submitted that the description of a multimer such as an immunoglobulin is so deficient in Goodman that the reference is non enabling on its face. The relevant disclosure in Goodman (col. 1, lines 62 to col. 2 line 7) is deficient, for example, because it does not discuss any of the factors that one should be aware of when attempting to obtain assembly of a functional multimeric protein. These factors include, for example,: 1) Methods for introducing the nucleic acid sequences encoding each of the polypeptides into the same host cell. Goodman is silent as to methods for co-transformation of multiple vectors or vectors containing more than one coding nucleic acid sequence; 2) Equivalent expression of each polypeptide chain, produced in sufficient concentration, in the same cellular compartment. Goodman fails to teach transcriptional and translational requirements for expressing multimeric proteins, such requirements being significantly different from the requirements for expressing a single polypeptide. For instance, the promoters operatively linked to the nucleic acid sequences should insure that mRNA expression occurs at the same level; 3) Each polypeptide should have a functional leader sequence which is processed along the protein secretory pathway via proteolytic cleavage; and 4) Methods which allow the regeneration the transformed cell in a manner that ensures that both genes are retained during the process. In view of these and other deficiencies, the mere mention to express a multimer such as an immunoglobulin in Goodman amounts to nothing more than an invitation to experiment. There can be no doubt that Goodman falls far short of overcoming the perceived prejudice in the art against expressing immunoglobulins in plants, as described in the attached Lerner declaration and discussed extensively above under the rejection for anticipation over During.

Accordingly, because Goodman fails to disclose each and every element of the claimed invention or is non-enabling, the rejection under §102(e) fails as a matter of law. The examiner, therefore, is respectfully urged to withdraw the rejection of the claims.

REJECTION UNDER 35 U.S.C. § 103 OVER DÜRING

The rejection of claims 21-40 and 42-68 under 35 U.S.C. § 103(a) as being allegedly obvious over Düring is respectfully traversed. Claims 42, 44-49, 51-53, and 64-68 have been cancelled herein, rendering the rejection moot as to these claims.

Relevant Law

A claimed invention is obvious if the differences between it and the prior art "are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103 (1994); see also Graham v. John Deere, 383 U.S. 1, 13 (1966).

Federal Circuit case law provides that "[t]he consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art." In re Dow Chem., 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed.Cir.1988). Under the law, there must be a showing of a suggestion, teaching, or motivation to combine the prior art references is an "essential evidentiary component of an obviousness holding." C.R. Bard, Inc. v. M3 Sys. Inc., 157 F.3d 1340, 1352, 48 USPQ2d 1225, 1232 (Fed.Cir.1998). Also required is that the combined teachings have a reasonable expectation of success, viewed in light of the prior art. *See* In re Dow Chemical Co., 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed.Cir.1988)("Both the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure.").

The examiner bears the burden of establishing a *prima facie* case of obviousness. In re Rijckaert, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed.Cir.1993); In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed.Cir.1992). This showing must be clear and particular, and broad conclusory statements about the teaching of

multiple references, standing alone, are not "evidence." *See* Dembiczak, 175 F.3d at 1000, 50 USPQ2d at 1617. However, the suggestion to combine need not be express and "may come from the prior art, as filtered through the knowledge of one skilled in the art." Motorola, Inc. v. Interdigital Technology Corp., 121 F.3d 1461, 1472, 43 USPQ2d 1481, 1489 (Fed.Cir.1997). Only when the examiner's burden is met does the burden of coming forward with rebuttal argument or evidence shift to applicant. Rijckaert, 9 F.3d at 1532, 28 USPQ2d at 1956.

Argument

To reiterate, the claims require the nucleic acid to encode a leader sequence for each polypeptide of the multimeric protein and that the leader sequence form a secretion signal which is cleaved following proteolytic processing. Also required is for the polypeptides to assemble in the plant cell resulting in formation of a multimeric protein which is a biologically functional multimer (i.e., "antigen-specific," in the case of immunoglobulin).

As already discussed above, the Lerner declaration demonstrates that there was a prejudice in the art against using plants to produce a processed and assembled immunoglobulin which is antigen specific, around the time of the During dissertation (*circa* 1988/1989). It was further demonstrated that the During dissertation was so lacking in proof that a person skilled in the art of immunology or protein expression, circa 1988/1989, would not have reasonably believed During's assertion that plant cells could be used to process and assemble an antigen-specific immunoglobulin. It is respectfully submitted that difficulties and deficiencies of During would , if anything, have strengthened rather than weakened this prejudice. Even assuming arguendo that there was no such prejudice in the art, During's conclusions would still not have been accepted by the ordinary skilled artisan, according to Lerner, who bases his view on extensive experience as an editorial board member of more than ten scientific journals and an official reviewer for hundreds articles submitted for publication. During's eventual publication of his antibody work in a peer-reviewed journal (i.e., 1990 article in "Plant Molecular Biology"), occurred after publication by the inventors (1989 article in "Nature"), extensively discussed the instant inventors' successful prior work. In Lerner's opinion,

this demonstrated that During's work was accepted for publication only because it was supported by the earlier published success of the instant inventors, Hiatt and Hein. Lerner credits the inventors of the instant patent application, not During, as the first to convincingly demonstrate assembly of an antigen-specific immunoglobulin in plant cells.

It is respectfully submitted, therefore, that the above noted deficiencies in the teachings of the During dissertation demonstrate overwhelmingly that no substantive foundation exists upon which to find any of the claims obvious over this reference.

Although the claims have not presently been rejected as obvious over the During dissertation in combination with any specified prior art teaching, it is also respectfully submitted that no such teachings or combination of teachings could cure the deficiencies noted for During. The only other reference raised for obviousness in this action is Goodman, but the teachings of this reference are, as described above under anticipation, similarly deficient to the During dissertation.

REJECTION UNDER 35 U.S.C. § 103 OVER GOODMAN

The rejection of claims 21-40 and 42-68 under 35 U.S.C. § 103(a) as being allegedly obvious over Goodman is respectfully traversed. Claims 42, 44-49, 51-53, and 64-68 have been cancelled herein, rendering the rejection moot as to these claims.

As already discussed under anticipation, Goodman's teachings at best are limited to expressing gamma interferon, a lymphokine that is a single polypeptide not a multimer. Gamma interferon also is functionally distinct from immunoglobulin and, moreover, Goodman teaches virtually nothing about immunoglobulin expression in plants. In fact, it is respectfully submitted that the description of a multimer such as an immunoglobulin is so deficient in Goodman as to be non enabling on its face. The relevant disclosure in Goodman (col. 1, lines 62 to col. 2 line 7) is deficient, for example, because it does not discuss any of the factors that one should be aware of when attempting to obtain assembly of a functional multimeric protein. These factors include, for example,: 1) Methods for introducing the nucleic acid sequences encoding each of the polypeptides into the same host cell. Goodman is silent as to methods for co-transformation of multiple

vectors or vectors containing more than one coding nucleic acid sequence; 2) Equivalent expression of each polypeptide chain, produced in sufficient concentration, in the same cellular compartment. Goodman fails to teach transcriptional and translational requirements for expressing multimeric proteins, such requirements being significantly different from the requirements for expressing a single polypeptide. For instance, the promoters operatively linked to the nucleic acid sequences should insure that mRNA expression occurs at the same level; 3) Each polypeptide should have a functional leader sequence which is processed along the protein secretory pathway via proteolytic cleavage; and 4) Methods which allow the regeneration the transformed cell in a manner that ensures that both genes are retained during the process. In view of these and other deficiencies, the mere mention to express a multimer such as an immunoglobulin in Goodman amounts to nothing more than an invitation to experiment. There can be no doubt that Goodman falls far short of overcoming the perceived prejudice in the art against expressing immunoglobulins in plants, as described in the attached Lerner declaration and discussed extensively above under the rejection for anticipation over During.

It is respectfully submitted, therefore, that the above noted deficiencies in the teachings of Goodman clearly demonstrate that no substantive foundation exists upon which to find the claims obvious over this reference. It is also submitted that no such teachings or combination of teachings exist that could cure the deficiencies noted for Düring. Moreover, as Applicants argued in the previous response, the unexpected results obtained from the instant invention was so surprising that the present inventor's work was featured on the cover of the prestigious journal Nature (see EXHIBIT 12 to the Lerner declaration).

CONCLUSION

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is urged to contact the undersigned by telephone to address any outstanding issues standing in the way of an allowance.

Respectfully submitted,

Date: March 20, 2002

By _____

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

21. (Amended two times) A plant, comprising:

(a) plant cells containing nucleotide sequences encoding one or more biologically functional multimeric proteins not normally produced by the plant, wherein each nucleotide sequence encoding a polypeptide of the multimeric protein encodes a leader sequence forming a secretion signal that is cleaved from said [~~multimeric protein~~] polypeptide following proteolytic processing; and

(b) biologically functional multimeric proteins encoded by said nucleotide sequences formed by assembly of said polypeptides in the cell.

31. (Amended) The plant of claim 21 wherein the multimeric protein comprises an immunoglobulin [~~product~~].

32. (Amended) The plant of claim 31 wherein the immunoglobulin [~~product~~] comprises [~~an~~] a Fab.

33. (Amended) The plant of claim 31 wherein the immunoglobulin [~~product~~] comprises [~~an~~] a Fab'.

34. (Amended) The plant of claim 31 wherein the immunoglobulin [~~product~~] comprises [~~an~~] a F(ab')2.

35. (Amended) The plant of claim 31 wherein the immunoglobulin [~~product~~] comprises an Fv.

36. (Amended) The plant of claim 31 wherein the immunoglobulin [~~product~~] comprises an antibody.

37. (Amended) The plant of claim 31 wherein the immunoglobulin [~~product~~] contains a paratope.

43. (Amended) A plant cell [~~that contains a nucleotide sequence that encodes a biologically functional multimeric protein not normally produced by the plant cell~~]

containing nucleotide sequences encoding an antigen-specific immunoglobulin, said nucleotide sequences encoding an immunoglobulin heavy and light chain polypeptide wherein each polypeptide contains a leader sequence that forms a secretion signal; and immunoglobulin encoded by said nucleotide sequences, wherein each leader sequence is cleaved from said immunoglobulin heavy chain and light chain polypeptide following proteolytic processing resulting in assembly of said antigen-specific immunoglobulin.

50. (Amended) The plant cell of claim 43 wherein the [~~multimeric protein~~] immunoglobulin is an abzyme.

54. (Amended) The plant cell of claim [53] 43 wherein the immunoglobulin [~~product~~] comprises [~~an~~] a Fab.

55. (Amended) The plant cell of claim [53] 43 wherein the immunoglobulin [~~product~~] comprises [~~an~~] a Fab'.

56. (Amended) The plant cell of claim [53] 43 wherein the immunoglobulin [~~product~~] comprises [~~an~~] a F(ab')2.

57. (Amended) The plant cell of claim [53] 43 wherein the immunoglobulin [~~product~~] comprises an Fv.

58. (Amended) The plant cell of claim [53] 43 wherein the immunoglobulin [~~product~~] comprises an antibody.

59. (Amended) The plant cell of claim [53] 43 wherein the immunoglobulin [~~product~~] contains a paratope.

60. (Amended) The plant cell of claim [53] 43 wherein the [~~multimeric protein comprises a~~] immunoglobulin is glycosylated, [~~immunoglobulin molecule~~] said glycosylation being free of sialic acid residues.